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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,570
Filing Date: May 02, 2002
Appellant(s): GODDARD ET AL.

Marc T. Morley
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/31/06 appealing from the Office action mailed 5/31/05.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Notice of Appeal filed in 10/063,647, 10/063,666, and 10/063,668.

Notice of Appeal and Appeal Brief filed in 10/063,514, 10/063,519, 10/063,524, 10/063,530, 10/063,534, 10/063,540, 10/063,578, 10/063,584, 10/063,586, 10/063,587, 10/063,591, 10/063,592, 10/063,607, 10/063,616, 10/063,617, 10/063,640, 10/063,648, 10/063,652, 10/063,653, 10/063,659, 10/063,660, and 10/063,661.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

This appeal involves claims 1-5.

Claim 6 has been canceled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal:

Chen et al. (2002), Mol. Cell. Proteomics 1.4: 304-313.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claims 1-5 are directed to antibodies that bind to polypeptides comprising SEQ ID NO: 64. The claimed antibodies are not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a real world" use for the claimed invention. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966):

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . .unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an appellant to engross what may prove to be a broad field.

The antibodies of the current invention bind to polypeptides comprising SEQ ID NO: 64. However, there is no utility for a polypeptide comprising SEQ ID NO: 64. Uses such as assaying for binding partners (p. 95), using polypeptides as molecular weight markers (p. 92), and screening for agonists and antagonists of PRO3566 (p. 95-99) are useful

only in research to determine the function of the encoded protein itself. There is no "specific benefit in currently available form" to be derived from such studies. Appellants also teach that the PRO3566 polypeptide or agonists or antagonists of PRO3566 may be used in the preparation of medicaments or in gene therapy (Examples 12 and 13). Even though Appellants teach that PRO3566 DNA is "more highly expressed" in normal skin cells and esophageal tumor cells when compared to melanoma tumor cells and normal esophageal cells, respectively (p. 142), there is no guidance in the specification as to how high the levels are. The asserted utility in diagnosis and treatment of the aforementioned cancers is not substantial. It is not clear whether the overexpression of PRO3566 is statistically significant and whether such overexpression is correlated to the overexpression of the encoded protein or whether it is due to aneuploidy. The specification fails to disclose the biological significance of this overexpression. The specification also does not teach whether the overexpression is the cause or the result of the tumors. The only thing Appellants teach is that the gene was "more highly expressed" and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. Clearly further research and experimentation would be required to find out whether PRO3566 is useful as asserted. See *Brenner v. Manson*, noting that "'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Further research would be required to determine how and if PRO3566 is involved in any disease.

The invention also lacks a well-established utility. A well-established utility is a

specific, substantial, and credible utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The specification fails to assert any activity for the polypeptide. Appellants have not asserted that PRO3566 is a member of any protein family nor have Appellants asserted that PRO3566 is homologous to any known proteins. Thus, PRO3566 lacks a well-established utility.

Claims 1-5 are rejected under 35 U.S.C. 1 12, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

Appellants argue that mRNA for the PRO3566 polypeptide is more highly expressed in normal skin compared to melanoma tumor, and in esophageal tumor compared to normal esophagus. Appellants further argue that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Appellants refer to a declaration of J. Christopher Grimaldi and argue that "the biological significance of the data, or the role of PRO3566 in cancer, is not necessary to use the claimed polypeptides as cancer diagnostic tools." Appellants argue that Exhibit 1 teaches that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Grimaldi states in section 6 that "I conducted a semi-quantitative analysis of the expression of the DNA sequences of interest in normal versus tumor tissues. Expression levels were graded

according to a scale of +, -, and +/- to indicate the amount of the specific signal detected. Using the widely accepted technique of PCR it was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same in tumor tissue as compared to its normal counterpart. Because this technique relies on the visual detection of ethidium bromide staining of PCR products on agarose gels, it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA." Furthermore, in another declaration of J. Christopher Grimaldi (Exhibit 4), Grimaldi states that when a gene is overexpressed, the gene product or polypeptide will also be overexpressed. The declaration of Dr. Paul Polakis avers that mRNA levels typically correlate with an increase in abundance of the encoded protein. Appellants further cite Orntoft et al., Hyman et al., and Pollack et al. in support of the argument that in the vast majority of cases, the combined teachings of the art teach that gene amplification influences gene expression and that gene expression influences protein levels. In addition, Appellants refer to the declaration of Dr. Ashkenazi and cited references Hanna and Mornin who teach that even if higher levels of mRNA do not correlate with an increase in abundance of the encoded protein, that type of information is also useful in diagnosing and treating patients.

Appellants' arguments have been fully considered but have not been found to be persuasive. A utility of being a diagnostic target for melanoma or esophageal tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use. This is not a substantial utility. In Example 30,

Appellants teach that PRO3566 was overexpressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus tissue. There is no guidance in the specification as to how high the levels of overexpression are. There is no information in the specification as to the differences in expression or whether the results were statistically significant. Appellants have provided no indication of the nature or number of samples that were used. The declaration of Grimaldi does not teach the level of reproducibility or the level of reliability of the results. If a clinician took a skin or esophageal tissue sample from a patient with suspected melanoma or esophageal cancer, what is the likelihood that when compared with normal tissue, the level of PRO3566 ***protein*** from the patient would be higher or lower? How many samples would be needed? What sensitivity would be needed? Appellants have provided no indication of the nature or number of samples that were used.

The only thing Appellants teach is that the gene was "more highly expressed" and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases. Appellants state that when a gene is overexpressed, the corresponding protein will generally also be overexpressed. However, Chen et al. teach that correlation between ***protein*** levels and ***mRNA*** expression can vary depending upon the protein (Chen et al. (2002), Mol. Cell. Proteomics 1.4: 304-313). Of 165 protein spots studied by Chen et al., only 17% of the samples showed a statistically significant correlation between mRNA and protein (p. 311). Some of the proteins actually demonstrated a negative correlation with the mRNA expression values (p. 311). One skilled in the art would need to do further research to determine whether or not the

PRO 3566 polypeptide levels increased or decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, *i.e.* it is not substantial. Without more specifics about necessary sample size, polypeptide expression level range for normal and tumor tissues, types of skin and esophageal tissue that can be used, and other questions, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary.

Appellants argue that the Examiner has not provided any evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. This is incorrect as the Examiner has provided the Chen et al. reference. In regards to the Grimaldi declarations, it is noted that Appellants argue that the Examiner has failed to establish a *prima facie* showing that a skilled artisan would reasonably doubt the asserted utility because the data in example 18 are sufficient to establish utility. In this regard Appellants refer to a declaration of Christopher Grimaldi (Exhibit 1). Appellants further argue that only the relative level of expression is important and that how high the level of expression is, is irrelevant. Appellants' arguments have been fully considered but they are not persuasive. The declaration of Christopher Grimaldi (Exhibit 1) has been considered. However, the assertions that "data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual" (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA" (paragraph 6), "the precise levels of gene expression are irrelevant" (paragraph 7), and "if a difference is detected, . . . the

gene and its corresponding polypeptide . . . are useful for diagnostic purposes" (paragraph 7) are conclusory and unsupported. Furthermore, the declaration does not provide any data concerning PRO3566 mRNA expression, PRO3566 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Contrary to Appellants' assertion that how high the level of expression is, is irrelevant, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. A gene whose change in expression is due to disease-independent differences between samples cannot be used as a diagnostic marker of the disease. Given the paucity of information regarding PRO3566 mRNA expression and the complete lack of data concerning PRO3566 polypeptide expression, a skilled artisan would regard the precise level of PRO3566 mRNA expression as relevant.

Regarding the Grimaldi declaration (Exhibit 1), Appellants argue that the examiner should accept Mr. Grimaldi' s opinion. This has been fully considered but is not found to be persuasive. In the instant case, the nature of the facts to be established are whether or not the change in PRO3566 transcripts is related to the disease or unrelated to the disease, whether or not there is a correlation between a change in PRO3566 transcripts and PRO3566 polypeptide expression in tumors, and if so, whether such a correlation could be used as a cancer diagnostic by use of the claimed antibodies. The skilled artisan would not know if the results seen in Example 18 were disease-dependent or disease-independent. Appellants have not provided any testing of the expression, role, or activity of the PRO3566 polypeptide. Even if the

Examiner were to assume that the present results with PRO3566 transcripts could reasonably be correlated with an assumed change in PRO3566 polypeptide expression, it still could not be ascertained if the assumed change in PRO3566 polypeptide expression would be disease-dependent or disease-independent because one would not know if the change in PRO3566 transcripts is disease-dependent or disease-independent. Furthermore, Appellants themselves have submitted the Gygi et al. (filed 5/6/05) reference which clearly states in the abstract (page 1720): "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold...Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient." Given that protein and mRNA levels can be unrelated over a range of 20 to 30-fold, it is the Examiner's position that the Appellants observed *2-fold* difference in mRNA levels is rather unpredictive of the encoded protein level, and it is this precise unpredictable protein level which the claimed antibodies would have to detect in order to possess the asserted utility.

Furthermore, Appellants have submitted a Hu et al. reference (filed 7/25/05) which states in its abstract (page 405) that "we found no correlation between the

strength of the literature association and the magnitude of the difference in expression level when considering changes as high as 5-fold; however, a significant correlation was observed ($r = 0.41$; $p = 0.05$) among genes showing an expression difference of 10-fold or more." Even with this more friendly assessment, Appellants 2-fold difference again falls short of the utility threshold.

Appellants argue that paragraphs 6 and 7 of the first declaration by Dr. Grimaldi explains that the semi-quantitative analysis used for Example 18 of the instant application is sufficient to determine if a gene is over- or under-expressed in a tumor compared to normal cell, with detectability of at least 2-fold differences, and the relative not the absolute difference is what matters. This argument has been fully considered but is not deemed persuasive. The conclusory statements in the declaration do not support a substantial utility or enable the invention because they do not fill important gaps in the disclosure needed to allow the skilled artisan to use the invention without significant further experimentation, such as expression level range for normal and tumor tissues, specific types of tumors detectable, and probability of detection for any particular tumor type (*e.g.*, whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested). Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues, this information does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as "semi-quantitative" and the specification for Example 18 as "standard quantitative". The declaration also says that

"Data from a pooled sample are more likely to be accurate than data from a single individual." This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of tissue that can used, and other questions, the specification has not provided the invention in an enabling or substantial form. Even if tissue samples are pooled, about which the first Grimaldi declaration says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance. If a clinician took a tissue sample from an individual patient with suspected cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of PRO3566 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? While the sixth paragraph of the first Grimaldi declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a specific and substantial use of the instant *antibodies* in the skilled artisan's

hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of tissue that can used, and other questions, the specification has not provided the invention in a form readily usable by the skilled such that *significant* further experimentation was unnecessary. Therefore, even accepting Dr. Grimaldi's opinion, the declaration is insufficient to overcome the rejection of the claims under 35 USC 101 and 112, first paragraph, for the reasons discussed above. It is noted that Dr. Grimaldi is an inventor of the instant application.

Appellants argue diagnosis of an individual's disease is based on disease indicators derived from characteristics of a populous. This argument has been fully considered but is not deemed persuasive because indicators are generally not from pooled samples but analysis of many individual samples. Thus the skilled clinical or researcher can analyze statistical significance as well as look for outliers, *etc.* As discussed in previous Office actions and above, one cannot tell from the pooled data of Example 18 probability of whether one would reasonably expect higher expression to be found in 10/10 or 1/20 tumors tested, for example.

Appellants argue that "Office personnel must accept opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questions." First, it is important to note that the instant specification provides no specific information regarding increased mRNA levels of PRO3566 in tumor samples relative to normal samples. Only gene expression data represented as "more highly expressed" was presented. Second, the declaration does not provide data such that the Examiner can

independently draw conclusions. Only Dr. Grimaldi's conclusions are provided in the declaration. While several articles are provided as evidentiary support to Dr. Grimladi's statement that it remains a dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, two of the references are discussed below and do not address the lack of substantial utility or enablement of antibodies to PRO3566 polypeptide. While one can find references that support Dr. Grimaldi's statements, other previously cited literature illustrates the unpredictability inherent in correspondence between mRNA and protein levels. Because of this inherent unpredictability in the art of record, significantly more guidance and teachings from the instant disclosure are required to place the invention into the hands of the public.

In the second Declaration of Dr. Grimaldi, Appellants argue that increased or decreased gene expression correlates with increased or decreased polypeptide expression, respectively, in a vast majority of the cases. Also, the declaration describes mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, not a readily available utility. The PRO3566 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the

development of cancer, nor has it been shown to be predictive of such. Similarly, unlike Her2/Neu, no chromosomal translocation of PRO3566 is known to occur. Paragraph 6 of the declaration says that even when amplification of a cancer marker gene does not result in significant over- or under-expression of the corresponding gene product, that in itself provides important information for cancer diagnosis and treatment. However, there is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. It remains that, as evidence by Haynes et al. and Fessler et al. (filed by Appellant on 7/25/05), for example, the issue is simply not predictable, and the specification presents a mere invitation to experiment. This is further borne out in paragraph 6, which proposes further experimentation, should Appellants' assertions be erroneous.

Appellants argue that the declaration by Dr. Polakis also submitted as an exhibit 1/31/06 supports both utility and enablement of the instant invention. In the declaration Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen

polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. The declaration does not provide data such that the Examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Appellants cite Alberts et al. (Molecular Biology of the Cell, 1994 and 2002, filed 1/31/06) for showing the steps at which eukaryotic gene expression can be controlled, correlating transcription with protein. This argument has been fully considered but is not deemed persuasive. It is noted that the field of proteomics was very new in 1994, when the first cited teachings of Alberts were published. Additionally, the references of Haynes et al. and Fessler et al. clearly show that one cannot reasonably expect that for any given mRNA the level of protein produced therefrom will correlate with the amount of mRNA.

Appellants also cite Lewin (Genes VI, 1997, filed 1/31/06) and Zhigang et al. (World J. Surg. Oncol, 2004, filed 1/31/06) to support the ideas of Alberts et al. (above), with the example of Zhigang et al. showing that there is a high correlation between PSCA protein and mRNA expression. This argument has been fully considered but is not deemed persuasive. Lewin teaches the same idea that Alberts et al. do. As Appellants quote Lewin, "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." Genes V1 at 847-848 (emphasis added by Examiner). Lewin says that one cannot presume a correlation between RNA and protein, even though most regulator events occur when DNA is transcribed. There is convincing evidence of record that in some cases transcription is the controlling factor but in other it is translation. Zhighan find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application we have no correlation. There is no suggestion in the specification of multiple tumors tested. There are just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO3566 nucleic acid and/or

protein. If Zhinghan et al. had obtained only a 5% correlation, it is doubtful he would have concluded that the nucleic acid would be a promising molecular marker.

Appellants argue that Meric et al. (Mol. Cancer Ther., 2002, filed 1/31/06) says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this statement is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use as discussed above and the art that teaches unpredictability concerning a correlation between protein and mRNA expression levels. Further reading of Meric et al. seems to teach away from Appellants' claim that there is a correlation between increased mRNA level and protein level. For example, Meric et al. discloses that variation in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974).

Appellants argue that the Examiner has dismissed textbook references, articles and declaration in maintaining the rejections. The argument has been fully considered, but is not persuasive. There are a number of significant unknowns in the specification that the declarations, exhibits and arguments do not solve. One example is that there are several types of cancers for any type of tissue, for example, squamus cell or adenocarcinoma, and the type which was identified in the instant application is not disclosed. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966) 696, in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists

> in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated previously, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a currently available form. Other gaps in information include, for example, tumor type (etiology), repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and a basis for reasonably expecting that a change in mRNA level causes a corresponding change in protein level.

Appellants argue that in *Brenner v. Manson*, 383 US 519, 148 USPQ 689 (1966) at 691, the Court held that "where a claimed process produces a known product it is not necessary to show utility for the product." Appellants say the Examiner points to no facts whatsoever in the decision to support the position that finding in *Brenner* are analogous to the instant application. The argument has been fully considered, but is not persuasive. Appellants' quote is taken from the reasoning of the court to allow an interference to proceed. The quoted idea of utility was what the Supreme Court set out to clarify and rectify with standing Court decisions. At 696, the Supreme Court stated that they "find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to

the process which yielded the unpatentable product." The Supreme Court also discussed (694):

> Even on the assumption that the process would be patentable were respondent to show that the steroid produced had a tumor-inhibiting effect in mice, [17]we would not overrule the Patent Office finding that respondent has not made such a showing. The Patent Office held that, despite the reference to the adjacent homologue, respondent's papers did not disclose a sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics. Indeed, respondent himself recognized that the presumption that adjacent homologues have the same utility [18]has been challenged in the steroid field because of "a greater known unpredictability of compounds in that field." [19]In these circumstances and in this technical area, we would not overturn the finding of the Primary Examiner, affirmed by the Board of Appeals and not challenged by the CCPA.

The above situation is analogous to that of the instant application because its claimed invention, the PRO3566 protein and related proteins have not been shown to have a sufficient likelihood of being used as a cancer diagnostic for the reasons previously discussed. Also, in the proteomic art there is a "known unpredictability" concerning the correlation of mRNA and protein levels.

Appellants discuss *In re Kirk (CCPA 1967)* in which the assertion that a man-made steroid with biological activity was insufficient without information in the specification as to how the biological activity could be practically used. This case does not refute the current rejections.

Appellants argue that in *Nelson v. Bowler*, the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. The argument has been fully considered, but is not persuasive. In *Nelson,* the court held that the compound of which utility was in

question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility because the specification does not allow the skilled artisan to use the instant invention for the reasons previously discussed. It is maintained that the instant application has not established a correlation between higher expression of the PRO3566 mRNA and polypeptide or the diagnostic use of the encoded protein.

Appellants argue that the Court in *Cross v. Iizuka* reaffirmed that a "rigorous correlation" is not required to establish practical utility. The argument has been fully considered, but is not persuasive. The Court (at 739) said, "a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence". At issue in *Cross* was practical utility, and the Court held that there is (often) a reasonable correlation between *in vitro* and *in vivo* activity. Neither the PRO3566 polynucleotide nor encoded polypeptide have been asserted to have a specific pharmacological activity. Instead they are said to have a specific diagnostic use. The arguments of pharmacological activity discussed in *Cross* and *Fujikawa* are, then, not directly related to the issues at hand.

Appellants also cite *Cross v. Iizuka* (Fed. Cir. 1985) and *Fujikawa v. Wattanasin* (Fed. Cir. 1996), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At

issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: whether differences in expression of PRO3566 nucleic acid were significant, under what conditions differences could be detected, repeatability of the differential expression of PRO3566 polynucleotide both in terms of frequency/prevalence and quantity/sensitivity, what levels (relative or absolute) were detected in tumors, and whether mRNA levels correlated with encoded protein levels, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention.

Turning to the rejection under 35 USC, 112, first paragraph enablement, Appellants argue that based in part on the disclosure in Example 18 of the instant application that the nucleic acid encoding the PRO3566 polypeptide is at least two-fold differentially expressed in tumor relative to normal tissue. The argument has been fully considered, but is not persuasive. There is nothing in Example 18 to indicate that the PRO3566 nucleic acid is two-fold differentially expressed. That opinion comes from the first declaration of Dr. Grimaldi. Further, even assuming it is two-fold differentially expressed, it is maintained for the reasons for record and as discussed above, that one of skill in the art would not reasonably expect that to be true of the PRO3566 protein because of the unpredictability of mRNA/protein level correlation studies in the art.

Appellants submit that because the claimed polypeptides have substantial, specific and credible utility, it is not proper to reject the claimed polypeptides as lacking enablement on a "lack of utility" basis. The argument has been fully considered, but is not persuasive. First, it is maintained that the invention does not have utility. Second, MPEP § 2107.01 states that "It is important to recognize that 35 U.S.C. 112, first paragraph, addresses matters other than those related to the question of whether or not an invention lacks utility. These matters include ... whether the applicant has provided an enabling disclosure of the claimed subject matter..."

Therefore, for reasons set forth above, Appellant's arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Stephen Gucker
May 15, 2006

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